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Harnessing the Elusive 1,4-Reduction of Vinyl Epoxides through Copper Catalysis

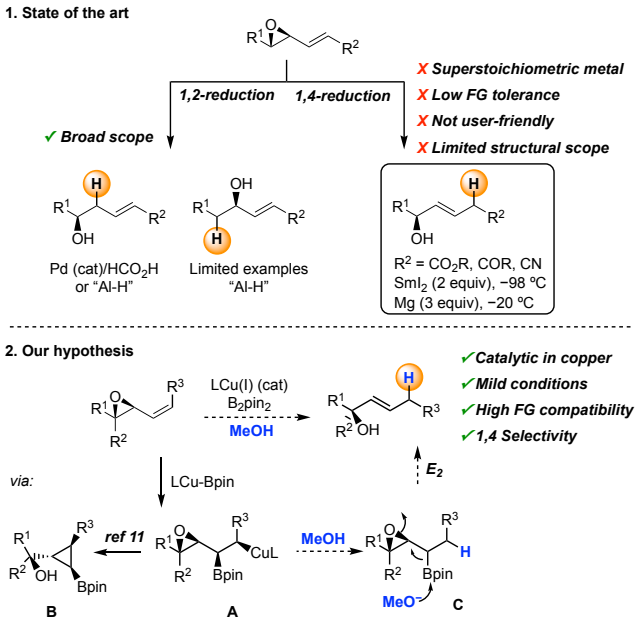
Laura Amenós, Luis Nóvoa, Laura Trulli, Ana Arroyo-Bondía, Alejandro Parra and Mariola Tortosa*

Organic Chemistry Department, Institute for Advance Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain.

ABSTRACT: We present an efficient strategy for the formal 1,4-reduction of vinyl epoxides that does not require superstoichiometric amounts of a strong reductant. Using a readily available copper catalyst and a diboron compound, a wide variety of enantioenriched allylic alcohols has been prepared. Additionally, epoxyenynes have been reduced in a 1,4-manner to selectively afford skipped enynes or skipped dienes.

KEYWORDS: vinyl epoxides, borylation, copper catalysis, allylic alcohols, skipped dienes.

Vinyl epoxides are attractive building blocks in organic synthesis. Their unique conjugation of the oxirane ring and a double bond makes them versatile electrophiles for a myriad of transformations.[1] Enantiomerically enriched vinyl epoxides can be easily prepared from dienes through asymmetric epoxidation or from α-epoxy alcohols through an oxidation-olefination sequence.[2] This availability makes them ideal substrates to prepare enantiomerically enriched compounds through reactions that enable chirality transfer. It is surprising, however, to find that one of the most intuitive transformations with these substrates, a simple reduction, remains largely unsolved. The reduction of vinyl epoxides can produce three different products, resulting from a 1,2-reduction (at either position of the epoxide) or a 1,4 pathway (Scheme 1). The palladium-catalyzed hydrogenolysis selectively reduces the epoxide at the allylic position (1,2-reduction), providing a robust method to prepare homoallylic alcohols (Scheme 1, left arrow).[3] The regioselectivity using aluminum and boron-based hydrides is highly dependent on the substrate. All three modes of ring opening have been observed, with most examples providing the 1,2-products.[4] Alternatively, the 1,4-reduction would provide access to chiral allylic alcohols (Scheme 2, right arrow). In the era of catalysis, it is remarkable to find that the two most general methods to achieve this transformation require superstoichiometric amounts of a metal and/or difficult to handle conditions.[5-7] In one of them, two equivalents of freshly prepared SmI_2 are used at a highly unpractical reaction temperature (–98 °C).[5] The second approach uses at least three equivalents of activated Mg in methanol at –20 °C.[6] Additionally, both methods are restricted to vinyl epoxides bearing a strong electron withdrawing group in the alkene. Moreover, functional groups such as ketones or alkyl and aryl halides are incompatible with these strong reductants.[8,9] Therefore, the development of a catalytic and mild method to perform the 1,4-reduction of vinyl epoxides is still an unmet challenge. A successful protocol would provide easy access to enantiomerically enriched allylic alcohols, which are important building blocks in synthetic chemistry.[10]



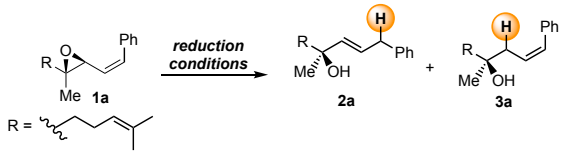
Scheme 1. Reduction of vinyl epoxides.

Recently, we used vinyl epoxides to prepare cyclopropylboronates **B** using a readily available copper(I) catalyst.[11] The catalytic cycle involved the formation of organocopper **A** from a vinyl epoxide and a copper-boryl complex, followed by an intramolecular S_N2-type reaction to provide **B**. We hypothesized that, in the presence of a proton source such as MeOH,[12] intermediate **A** would be intercepted before cyclization to afford epoxy boronate **C**. This intermediate could undergo a base-promoted β-oxygen elimination to give the formal reduction product.[13] This approach would provide a mild and catalytic method to reduce vinyl epoxides in a 1,4-manner, without using superstoichiometric amounts of a strong reductant.

To test our hypothesis, we selected vinyl epoxide **1a**, previously used in our cyclopropane synthesis.[11,14] This starting point was of particular interest given that the 1,4-reduction of vinyl epoxides with a simple aryl group in the double bond is virtually unknown in the literature.[15] Gratifyingly, with similar conditions to those used for the cyclopropanes, in the presence of a proton source, we observed the formation of allylic alcohol **2a** as a single *E*-isomer (Table 1, entry 1). This result indicated that

the elimination proposed in Scheme 1 occurs spontaneously and with stereocontrol. Next, we compared our conditions with other reducing agents typically used with vinyl epoxides. As expected, $LiAlH_4$ cleanly provided homoallylic alcohol **3a** (Table 1, entry 2). The used of SmI_2 (2 equiv), under the conditions described in the literature, provided a complex mixture (Table 1, entry 3) from which we could not identify the 1,4-reduction product. Moreover, activated Mg in MeOH gave a mixture of the reduced 1,2- and 1,4-products with poor regioselectivity (Table 1, entry 4). Surprisingly, epoxide **1a** did not react upon addition of BH_3 (Table 1, entry 5).[4b] Finally, we tried conditions to generate copper hydride species, that have shown to be effective for the 1,4-reduction of propargylic epoxides.[16] Unfortunately, we recovered unreacted epoxide, either using IPrCuCl or $Cu(OAc)_2$ with 1,2-bis(diphenylphosphino)benzene (dppbz) as ligand (Table 1, entries 6,7).

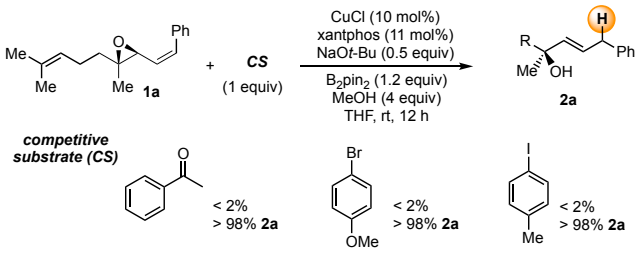
Table 1. 1,4-Reduction of vinyl epoxides under different conditions.



Entry	Conditions	**2a**:**3a**	Yield (%)[a]
1	**A**: CuCl (10 mol%), xantphos (11 mol%), NaO*t*-Bu (0.5 equiv), B_2pin_2 (1.2 equiv), MeOH (4 equiv), THF, 12 h, rt	100:0	75
2	**B**: $LiAlH_4$, THF, 0 °C	0:100	61
3	**C**: SmI_2 (2 equiv), THF/MeOH, –90 °C, 1 h	–	–[b]
4	**D**: Mg (3 equiv), MeOH, –20 °C, 2 h	75:25	72
5	**E**: BH_3·THF (2 equiv), THF	–	–[c]
6	**F**: IPrCuCl (10 mol%), NaO*t*-Bu (30 mol%), PMHS (2 equiv), toluene	–	–[c]
7	**G**: $Cu(OAc)_2$ (10 mol%), NaO*t*-Bu (30 mol%), dppbz, PMHS (2 equiv), toluene	–	–[c]

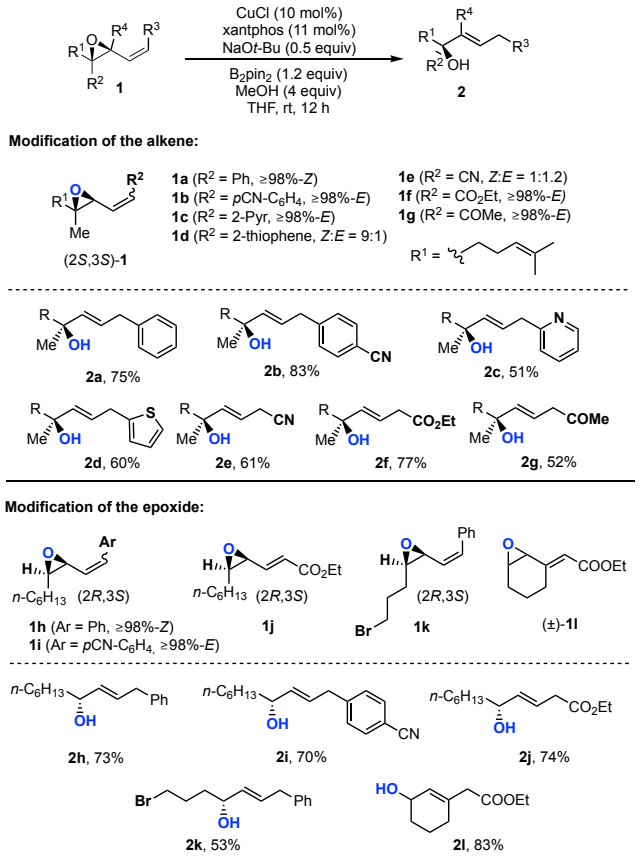
[a]Isolated yields. [b]Complex mixture. [c]Unreacted starting material.

To further compare our method with the use of SmI_2 or Mg/MeOH, we tested our conditions in the presence of three functional groups that are incompatible with these reductants (Scheme 2). We set up the reaction of **1a** under the conditions described in table 1 (entry 1), in the presence of 1 equivalent of a ketone, an aryl bromide or an aryl iodide. Pleasingly, in all of three cases we observed clean conversion of epoxide **1a** to allylic alcohol **2a**, without detecting significant borylation of the competitive substrate (<2% of borylation).[17]



Scheme 2. Functional group compatibility.

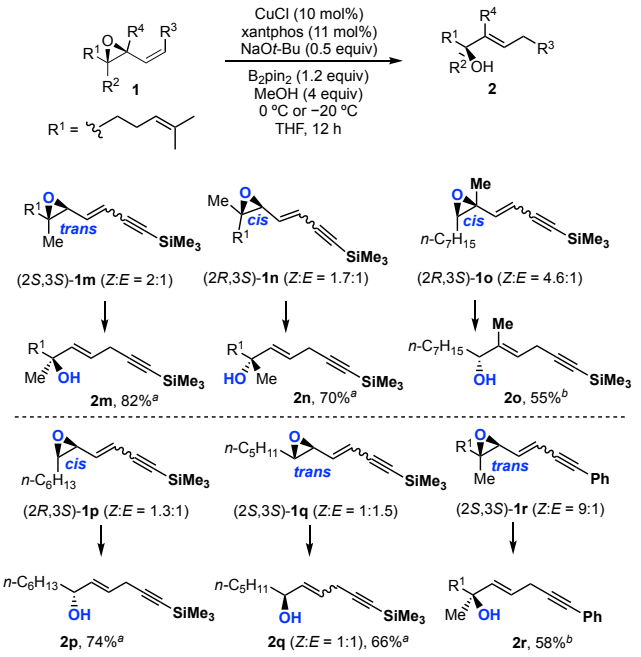
We next studied the generality of the method with different vinyl epoxides (Scheme 3). The reduction worked smoothly for vinyl epoxides bearing different aromatic groups on the alkene (**1a-1d**, Scheme 3), including heterocycles such as pyridine (**2c**) and thiophene (**2d**). The method is also effective for epoxides bearing -CN, $-CO_2R$ and -COR groups in the double bond (**1e-1g**). Compounds **2e**, **2f** and **2g** were prepared with efficiencies comparable to those observed with SmI_2 or Mg/MeOH. Moreover, disubstituted epoxides (**1h-1l**) afforded the corresponding allylic alcohols (**2h-2l**) in good yields as single *E*-isomers. It is worth highlighting that epoxide **1k** provided allylic alcohol **2k** preserving the sensitive primary alkyl bromide.[18] This example shows the exquisite selectivity of our method and its potential to be used with highly functionalized intermediates. Additionally, cyclic epoxide **1l** was also a suitable substrate for the 1,4-reduction.



Scheme 3. Scope of the copper-catalyzed formal 1,4-reduction of vinyl epoxides.

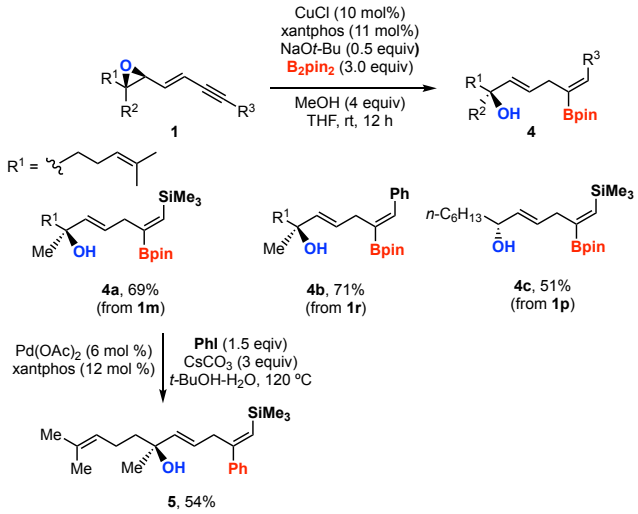
We then turned our attention to epoxyenynes **1m**-**1r**, a different class of vinyl epoxides, bearing a versatile alkyne attached to the double bond (Scheme 4). We were interested in the reduction of these compounds for three main reasons: 1) Epoxyenynes have never been selectively reduced in a 1,4-manner before. Previous attempts to do so resulted in 1,2-reduction,[19] allene formation or decomposition of the starting material.[20] 2) The products would be enantiomerically enriched skipped enynes, versatile building blocks that can be further functionalized through different stereoselective transformations.[21] 3) Chemoselectivity is tested to the limit with these starting materials, since alkynes are known to react smoothly under copper-catalyzed borylation conditions.[22]

When we applied the optimized conditions to *trans*-epoxyenyne **1m**, at 0 °C, we observed exclusive 1,4-reduction of the vinyl epoxide unit, without detecting borylation of the alkyne (Scheme 4). The corresponding *cis*-epoxide **1n** provided allylic alcohol **2n** as a single *E*-isomer, with similar efficiency. In both cases, the starting epoxyenynes were conveniently prepared and used as mixtures of *E*/*Z* isomers in the alkene, without affecting the outcome of the transformation. Interestingly, epoxide **1o** afforded skipped enyne **2o**, with a challenging trisubstituted *E*-olefin. *Cis* and *trans* disubstituted epoxyenynes **1p** and **1q** were also tested. Although both compounds provided the 1,4-reduction product in high yield, we observed that the substitution at R^2 of the epoxide ($R^2 \neq H$) was necessary to control the *E*/*Z* geometry of the newly formed double bond in the products. Moreover, skipped diene **2r**, with a phenyl group in the alkyne, was also prepared with high chemo- and stereocontrol.[23]



Scheme 4. 1,4-Reduction of epoxy enynes. [a]Reaction carried out at 0 °C. [b]Reaction carried out at −20 °C.

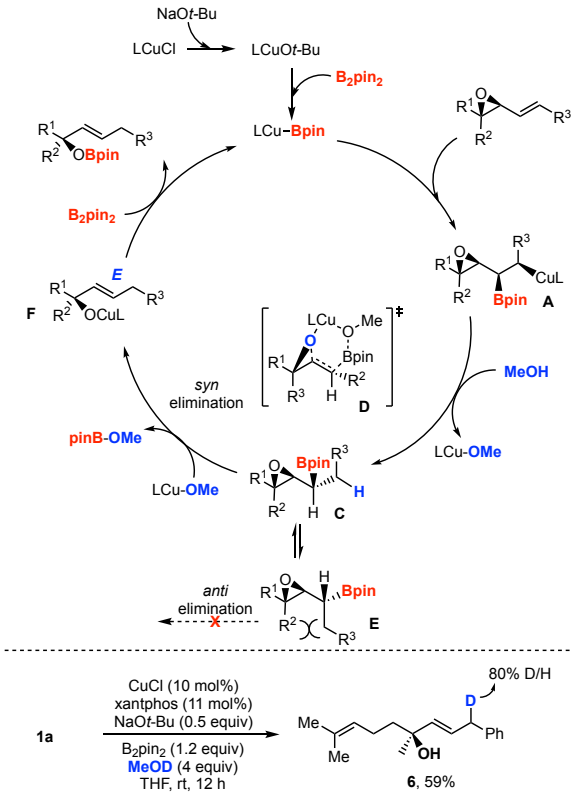
When the 1,4-reduction of epoxyenynes was performed at room temperature, we could identify variable amounts of the product derived from the borylation of the alkyne in compounds **2**. This observation encouraged us to pursue a reduction-borylation sequence to prepare functionalized skipped dienes (Scheme 5). Indeed, we were pleased to find that using 3 equivalents of the diboron reagent at room temperature, under otherwise identical conditions, skipped dienes **4a**, **4b** and **4c** were obtained in good yields as single regio- and stereoisomers.



Scheme 5. Synthesis of bifunctional skipped dienes.

These results showed that the 1,4-reduction of the vinyl epoxide moiety takes place first, followed by a regioselective monoborylation of the alkyne. This order is a crucial factor to control the regioselectivity in the borylation of the alkyne. Skipped dienes **4a** and **4c** are particularly attractive molecules because they have a bifunctional boron-silicon alkene, that could be selectively functionalized through orthogonal cross-coupling reactions.[24] To demonstrate this concept with our compounds, diene **4a** was transformed into functionalized skipped diene **5** through a selective Suzuki-Miyaura reaction.

A plausible mechanism for the 1,4-reduction of vinyl epoxides is outlined in Scheme 6. The catalytically active copper(I)-boryl complex is formed first, followed by insertion of the alkene of the vinyl epoxide into the Cu-B bond to form intermediate **A**. According to our previous observations in the cyclopropane formation,[11] we assumed a *syn* approach of the copper-boryl complex to the vinyl epoxide in an *s*-trans conformation (as shown in Scheme 6). Protonation of intermediate **A** prevents cyclization and provides epoxy boronate **C**.[25] From intermediate **C** a *syn*- elimination process would justify the *E* geometry of the newly formed double bond. We believe this *syn*-elimination could be promoted by the copper methoxide present in the media through transition state **D**. When $R^2 \neq H$, the conformer leading to the *anti*-elimination product (conformer **E**), would present a disfavorable 1,5-*syn* pentane-type interaction. When $R^2 = H$, this interaction is reduced and both elimination pathways could compete. This mechanistic pathway is reinforced by the result observed for epoxide **1q** ($R^2 = H$, Scheme 4), for which a mixture of *Z*/*E* products was observed. After ring opening, copper-alkoxide **F** is formed. This intermediate would restart the catalytic cycle through reaction with the diboron compound. To support this mechanism, the reduction of **1m** was carried out in the presence of deuterated methanol (MeOD), affording deuterated compound **6** with 80% deuterium incorporation at the allylic-benzylic carbon.



Scheme 6. Proposed mechanism.

In summary, we have developed a catalytic 1,4-reduction of vinyl epoxides using an inexpensive and readily available copper(I) catalyst, through a novel mechanistic pathway. Compared with other methods, our conditions are mild, easy-to-handle and show high functional group tolerance. With these conditions, challenging epoxyenynes have been 1,4-reduced for the first time to selectively produce skipped enynes or skipped dienes, the later with a bifunctional alkene amenable for orthogonal cross-coupling transformations.

AUTHOR INFORMATION

Corresponding Author

E-mail: mariola.tortosa@uam.es

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information is available free of charge via the Internet at http://pubs.acs.org."
Procedures and characterization data (PDF).

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